CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074644

Trade Name : METOPROLOL TARTRATE

Generic Name: Metaprolol Tartrate

Sponsor : Caraco Pharmaceuticals Ltd

Approval Date: December 10, 1996

ANDA 74-644

Caraco Pharmaceutical Laboratories, Ltd.
Attention: Annie Holt
1150 Elijah McCoy Drive
Detroit, Michigan 48202

Dear Ms. Holt:

This is in reference to your abbreviated new drug application dated March 8, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Metoprolol Tartrate Tablets USP, 50 mg and 100 mg.

Reference is also made to your amendments dated January 25, 1996 and September 27, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Metoprolol Tartrate Tablets USP, 50 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Lopressor® Tablets, 50 mg and 100 mg, respectively, of Geigy Pharmaceuticals). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

D L. Sporn 12/10/96

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMIST'S REVIEW NO. 3

2. ANDA # 74-644

3. NAME AND ADDRESS OF APPLICANT
Caraco Pharmaceutical Laboratories, Ltd.
1150 Elijah McCoy Drive
Detroit, Michigan 48202

4. LEGAL BASIS for ANDA SUBMISSION
LOPRESSOR® Tablets - 50 mg/tablet
LOPRESSOR® Tablets - 100 mg/tablet
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME

7. NONPROPRIETARY NAME
Metoprolol Tartrate USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Firm:

3/8/95	Original submission.
1/10/96	Amendment - Response to Agency's letter of 8/24/95.
1/25/96	Amendment - Response to Agency's biodeficiency letter of 11/29/95.
9/27/96	**Amendment - Response to Agency's letter of 7/30/96.**

FDA:

4/4/95	Receipt acknowledged.
8/24/95	Issuance of Not Approvable letter.
11/29/95	Issuance of Biodeficiency letter.
5/13/96	Issuance of Bioequivalence No Further Questions letter.
7/30/96	Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY
Antihypertensive

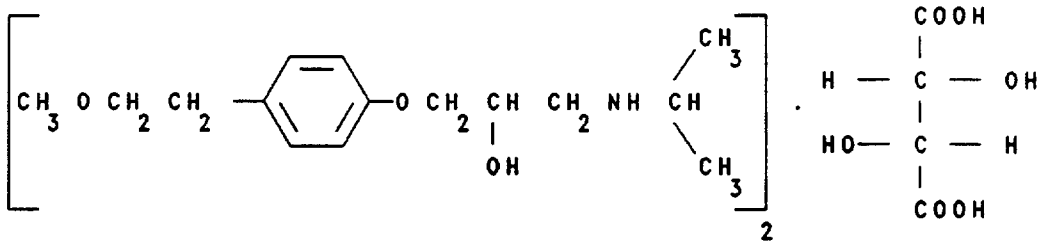
11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Coated tablet for oral administration

14. POTENCIES
50 mg/tablet
100 mg/tablet

15. CHEMICAL NAME AND STRUCTURE



(±)-1-(isopropylamino)-3-[p-(2-methoxyethyl)phenoxy]-2-propanol (2:1) *dextro*-tartrate salt

1-[4-(2-Methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol (2:1) *dextro*-tartrate salt

Molecular Formula: $C_{34}H_{56}N_2O_{12}$

Molecular Weight: 684.82

Metoprolol Tartrate is a white, practically odorless, crystalline powder. It is very soluble in water (>1000 mg/mL @ 25°C), freely soluble in methylene chloride, in chloroform, and in alcohol, slightly soluble in acetone, and insoluble in ether.

16. RECORDS AND REPORTS
7/24/95 - Chemistry Review #1, G.J. Smith.
7/24/95 - Labeling Review, J. Grace.
5/13/96 - Bioequivalence Review, J. Lee.
6/25/96 - Chemistry Review #2, G.J. Smith.
10/9/96 - Labeling Review, C. Hoppes.

17. COMMENTS
The firm has resolved all major questions regarding the chemistry, manufacturing and and controls section of the application.

Labeling was found to be satisfactory.

The Division of Bioequivalence found the drug product equivalent and granted waiver.

EER submitted and pending. GIK 12/2/96

Methods validation not required since drug substance and product are compendial.

DMF for drug substance remains satisfactory.

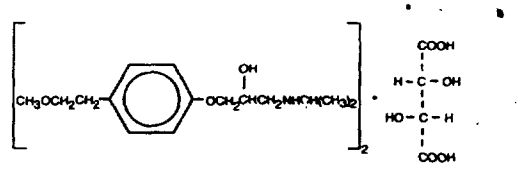
18. CONCLUSIONS AND RECOMMENDATIONS
The application may be Approved, pending satisfactory EIR. GIK

19. REVIEWER: Glen Jon Smith

Metoprolol Tartrate Tablets USP

DESCRIPTION

Metoprolol tartrate is a selective $beta_1$-adrenoreceptor blocking agent, available as 50 and 100 mg tablets for oral administration. Metoprolol tartrate is (±)-1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol (2:1) *dextro*-tartrate salt, and its structural formula is:



$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6$

Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

Inactive Ingredients. Tablets contain colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate, povidone, sodium starch glycolate, talc and titanium dioxide.

CLINICAL PHARMACOLOGY

Metoprolol tartrate is a beta-adrenergic receptor blocking agent, *in vitro* and *in vivo* animal studies have shown that it has a preferential effect on $beta_1$ adrenoreceptors, chiefly located in cardiac muscle. This preferential effect is not absolute, however, and at higher doses, metoprolol also inhibits $beta_2$ adrenoreceptors, chiefly located in the bronchial and vascular musculature.

Clinical pharmacology studies have confirmed the beta-blocking activity of metoprolol in man, as shown by (1) reduction in heart rate and cardiac output at rest and upon exercise, (2) reduction of systolic blood pressure upon exercise, (3) inhibition of isoproterenol-induced tachycardia, and (4) reduction of reflex orthostatic tachycardia.

Relative $beta_1$ selectivity has been confirmed by the following: (1) In normal subjects, metoprolol is unable to reverse the $beta_2$-mediated vasodilating effects of epinephrine. This contrasts with the effect of nonselective ($beta_1$ plus $beta_2$) beta blockers, which completely reverse the vasodilating effects of epinephrine. (2) In asthmatic patients, metoprolol reduces FEV_1 and FVC significantly less than a nonselective beta blocker, propranolol, at equivalent $beta_1$-receptor blocking doses.

Metoprolol has no intrinsic sympathomimetic activity, and membrane-stabilizing activity is detectable only at doses much greater than required for beta blockade. Metoprolol crosses the blood-brain barrier and has been reported in the CSF in a concentration 78% of the simultaneous plasma concentration. Animal and human experiments indicate that metoprolol slows the sinus rate and decreases AV nodal conduction.

In controlled clinical studies, metoprolol tartrate has been shown to be an effective antihypertensive agent when used alone or as concomitant therapy with thiazide-type diuretics, at dosages of 100 to 450 mg daily. In controlled, comparative, clinical studies, metoprolol has been shown to be as effective an antihypertensive agent as propranolol, methyldopa, and thiazide-type diuretics, and to be equally effective in supine and standing positions.

The mechanism of the antihypertensive effects of beta-blocking agents has not been elucidated. However, several possible mechanisms have been proposed: (1) competitive antagonism of catecholamines at peripheral (especially cardiac) adrenergic neuron sites, leading to decreased cardiac output; (2) a central effect leading to reduced sympathetic outflow to the periphery; and (3) suppression of renin activity.

By blocking catecholamine-induced increases in heart rate, in velocity and extent of myocardial contraction, and in blood pressure, metoprolol reduces the oxygen requirements of the heart at any given level of effort, thus making it useful in the long-term management of angina pectoris. However, in patients with heart failure, beta-adrenergic blockade may increase oxygen requirements by increasing left ventricular fiber length and end-diastolic pressure.

Although beta-adrenergic receptor blockade is useful in the treatment of angina and hypertension, there are situations in which sympathetic stimulation is vital. In patients with severely damaged hearts, adequate ventricular function may depend on sympathetic drive. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. $Beta_2$-adrenergic blockade results in passive bronchial constriction by interfering with endogenous adrenergic bronchodilator activity in patients subject to bronchospasm and may also interfere with exogenous bronchodilators in such patients.

In controlled clinical trials, metoprolol tartrate administered two or four times daily, has been shown to be an effective antianginal agent, reducing the number of angina attacks and increasing exercise tolerance. The dosage used in these studies ranged from 100 to 400 mg daily. A controlled, comparative, clinical trial showed that metoprolol was indistinguishable from propranolol in the treatment of angina pectoris.

In a large (1,395 patients randomized), double-blind, placebo-controlled clinical study, metoprolol was shown to reduce 3-month mortality by 36% in patients with suspected or definite myocardial infarction.

Patients were randomized and treated as soon as possible after their arrival in the hospital, once their clinical condition had stabilized and their hemodynamic status had been carefully evaluated. Subjects were ineligible if they had hypotension, bradycardia, peripheral signs of shock, and/or more than minimal basal rales as signs of congestive heart failure. Initial treatment consisted of intravenous followed by oral administration of metoprolol tartrate or placebo, given in a coronary care or comparable unit. Oral maintenance therapy with metoprolol or placebo was then continued for 3 months. After this double-blind period, all patients were given metoprolol and followed up to 1 year.

The median delay from the onset of symptoms to the initiation of therapy was 8 hours in both the metoprolol and placebo treatment groups. Among patients treated with metoprolol, there were comparable reductions in 3-month mortality for those treated early (≤ 8 hours) and those in whom treatment was started later. Significant reductions in the incidence of ventricular fibrillation and in chest pain following initial intravenous therapy were also observed with metoprolol and were independent of the interval between onset of symptoms and initiation of therapy.

The precise mechanism of action of metoprolol in patients with suspected or definite myocardial infarction is not known.

In this study, patients treated with metoprolol received the drug both very early (intravenously) and during a subsequent 3-month period, while placebo patients received no beta-blocker treatment for this period. The study thus was able to show a benefit from the overall metoprolol regimen but cannot separate the benefit of very early intravenous treatment from the benefit of later beta-blocker therapy. Nonetheless, because the overall regimen showed a clear beneficial effect on survival without evidence of an early adverse effect on survival, one acceptable dosage regimen is the precise regimen used in the trial. Because the specific benefit of very early treatment remains to be defined however, it is also reasonable to administer the drug orally to patients at a later time as is recommended for certain other beta blockers.

Pharmacokinetics

In man, absorption of metoprolol is rapid and complete. Plasma levels following oral administration, however, approximate 50% of levels following intravenous administration, indicating about 50% first-pass metabolism.

Plasma levels achieved are highly variable after oral administration. Only a small fraction of the drug (about 12%) is bound to human serum albumin. Elimination is mainly by biotransformation in the liver, and the plasma half-life ranges from approximately 3 to 7 hours. Less than 5% of an oral dose of metoprolol is recovered unchanged in the urine; the rest is excreted by the kidneys as metabolites that appear to have no clinical significance. The systemic availability and half-life of metoprolol in patients with renal failure do not differ to a clinically significant degree from those in normal subjects. Consequently, no reduction in dosage is usually needed in patients with chronic renal failure.

Significant beta-blocking effect (as measured by reduction of exercise heart rate) occurs within 1 hour after oral administration, and its duration is dose-related. For example, a 50% reduction of the maximum registered effect after single oral doses of 20, 50, and 100 mg occurred at 3.3, 5.0, and 6.4 hours, respectively, in normal subjects. After repeated oral dosages of 100 mg twice daily, a significant reduction in exercise systolic blood pressure was evident at 12 hours.

Equivalent maximal beta-blocking effect is achieved with oral and intravenous doses in the ratio of approximately 2.5:1.

There is a linear relationship between the log of plasma levels and reduction of exercise heart rate. However, antihypertensive activity does not appear to be related to plasma levels. Because of variable plasma levels attained with a given dose and lack of a consistent relationship of antihypertensive activity to dose, selection of proper dosage requires individual titration.

In several studies of patients with acute myocardial infarction, intravenous followed by oral administration of metoprolol caused a reduction in heart rate, systolic blood pressure, and cardiac output. Stroke volume, diastolic blood pressure, and pulmonary artery end diastolic pressure remained unchanged.

In patients with angina pectoris, plasma concentration measured at 1 hour is linearly related to the oral dose within the range of 50 to 400 mg. Exercise heart rate and systolic blood pressure are reduced in relation to the logarithm of the oral dose of metoprolol. The increase in exercise capacity and the reduction in left ventricular ischemia are also significantly related to the logarithm of the oral dose.

INDICATIONS AND USAGE

Hypertension

Metoprolol tartrate tablets are indicated for the treatment of hypertension. They may be used alone or in combination with other antihypertensive agents.

Angina Pectoris

Metoprolol tartrate tablets are indicated in the long-term treatment of angina pectoris.

Myocardial Infarction

Metoprolol tartrate injection and tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute myocardial infarction to reduce cardiovascular mortality. Treatment with intravenous metoprolol tartrate can be initiated as soon as the patient's clinical condition allows (see DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS). Alternatively, treatment can begin within 3 to 10 days of the acute event (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Hypertension and Angina

Metoprolol tartrate is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see WARNINGS).

Myocardial Infarction

Metoprolol is contraindicated in patients with a heart rate < 45 beats/min; second- and third-degree heart block; significant first-degree heart block (P-R interval ≥ 0.24 sec); systolic blood pressure < 100 mmHg; or moderate-to-severe cardiac failure (see WARNINGS).

WARNINGS

Hypertension and Angina

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive and angina patients who have congestive heart failure controlled by digitalis and diuretics, metoprolol should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic. The response should be observed closely. If cardiac failure continues, despite adequate digitalization and diuretic therapy, metoprolol should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have occurred. When discontinuing chronically administered metoprolol, particularly in patients with ischemic heart disease, the dosage should be gradually reduced over a period of 1 to 2 weeks and the patient should be carefully monitored. If angina markedly worsens or acute coronary insufficiency develops, metoprolol administration should be reinstates promptly, at least temporarily, and other measures appropriate for the management of unstable angina should be taken. Patients should be warned against interruption or discontinuation of therapy without the physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue metoprolol therapy abruptly even in patients treated only for hypertension.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative $beta_1$ selectivity, however, metoprolol may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since $beta_1$ selectivity is not absolute, a $beta_2$ stimulating agent should be administered concomitantly, and the lowest possible dose of metoprolol tartrate should be used. In these circumstances it would be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (SEE DOSAGE AND ADMINISTRATION.)**

Major Surgery: The necessity or desirability of withdrawing beta-blocking therapy prior to major surgery is controversial; the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists, and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes and Hypoglycemia: Metoprolol should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade, which might precipitate a thyroid storm.

Myocardial Infarction

Cardiac Failure: Sympathetic stimulation is a vital component supporting circulatory function, and beta blockade carries the potential hazard of depressing myocardial contractility and precipitating or exacerbating minimal cardiac failure.

During treatment with metoprolol, the hemodynamic status of the patient should be carefully monitored. If heart failure occurs or persists despite appropriate treatment, metoprolol should be discontinued.

Bradycardia: Metoprolol produces a decrease in sinus heart rate in most patients; this decrease is greatest among patients with high initial heart rates and least among patients with low initial heart rates. Acute myocardial infarction (particularly inferior infarction) may in itself produce significant lowering of the sinus rate. If the sinus rate decreases to < 40 beats/min, particularly if associated with evidence of lowered cardiac output, atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, metoprolol should be discontinued, and cautious administration of isoproterenol or installation of a cardiac pace-maker should be considered.

AV Block: Metoprolol slows AV conduction and may produce significant first- (P-R interval ≥ 0.26 sec), second-, or third-degree heart block. Acute myocardial infarction also produces heart block.

If heart block occurs, metoprolol should be discontinued and atropine (0.25 to 0.5 mg) should be administered intravenously. If treatment with atropine is not successful, cautious administration of isoproterenol or installation of a cardiac pacemaker should be considered.

Hypotension: If hypotension (systolic blood pressure ≤ 90 mmHg) occurs, metoprolol should be discontinued, and the hemodynamic status of the patient and the extent of myocardial damage carefully assessed. Invasive monitoring of central venous, pulmonary capillary wedge, and arterial pressures may be required. Appropriate therapy with fluids, positive inotropic agents, balloon counterpulsation, or other treatment modalities should be instituted. If hypotension is associated with sinus bradycardia or AV block, treatment should be directed at reversing these (see above).

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD, IN**

GENERAL, NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, metoprolol may be used with extreme caution in patients with bronchospastic disease. Because it is unknown to what extent beta$_2$-stimulating agents may exacerbate myocardial ischemia and the extent of infarction, these agents should not be used prophylactically. If bronchospasm not related to congestive heart failure occurs, metoprolol should be discontinued. A theophylline derivative or a beta$_2$ agonist may be administered cautiously, depending on the clinical condition of the patient. Both theophylline derivatives and beta$_2$ agonists may produce serious cardiac arrhythmias.

PRECAUTIONS

General

Metoprolol should be used with caution in patients with impaired hepatic function.

Information for Patients

Patients should be advised to take metoprolol regularly and continuously, as directed, with or immediately following meals. If a dose should be missed, the patient should take only the next scheduled dose (without doubling it). Patients should not discontinue metoprolol without consulting the physician.

Patients should be advised (1) to avoid operating automobiles and machinery or engaging in other tasks requiring alertness until the patient's response to therapy with metoprolol has been determined; (2) to contact the physician if any difficulty in breathing occurs; (3) to inform the physician or dentist before any type of surgery that he or she is taking metoprolol.

Laboratory Tests

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug Interactions

Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with metoprolol plus a catecholamine depletor should therefore be closely observed for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Risk of Anaphylactic Reaction. While taking beta-blockers, patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge, either accidental, diagnostic, or therapeutic. Such patients may be unresponsive to the usual doses of epinephrine used to treat allergic reaction.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have been conducted to evaluate carcinogenic potential. In a 2-year study in rats at three oral dosage levels of up to 800 mg/kg per day, there was no increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes that appeared to be drug related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. In a 21-month study in Swiss albino mice at three oral dosage levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant or total (benign plus malignant) lung tumors, nor in the overall incidence of tumors or malignant tumors. This 21-month study was repeated in CD-1 mice, and no statistically or biologically significant differences were observed between treated and control mice of either sex for any type of tumor.

All mutagenicity tests performed (a dominant lethal study in mice, chromosome studies in somatic cells, a Salmonella/mammalian-microsome mutagenicity test, and a nucleus anomaly test in somatic interphase nuclei) were negative.

No evidence of impaired fertility due to metoprolol was observed in a study performed in rats at doses up to 55.5 times the maximum daily human dose of 450 mg.

Pregnancy Category C

Metoprolol has been shown to increase postimplantation loss and decrease neonatal survival in rats at doses up to 55.5 times the maximum daily human dose of 450 mg. Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. These studies have revealed no evidence of impaired fertility or teratogenicity. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Metoprolol is excreted in breast milk in very small quantity. An infant consuming 1 liter of breast milk daily would receive a dose of less than 1 mg of the drug. Caution should be exercised when metoprolol is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypertension and Angina

Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression has been reported in about 5 of 100 patients. Mental confusion and short-term memory loss have been reported. Headache, nightmares, and insomnia have also been reported.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency, usually of the Raynaud type; palpitations; congestive heart failure;peripheral edema; and hypotension have been reported in about 1 of 100 patients. (See CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS.)

Respiratory: Wheezing (bronchospasm) and dyspnea have been reported in about 1 of 100 patients (see WARNINGS).

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, dry mouth, gastric pain, constipation, flatulence, and heartburn have been reported in about 1 of 100 patients.

Hypersensitive Reactions: Pruritus or rash have occurred in about 5 of 100 patients. Worsening of psoriasis has also been reported.

Miscellaneous: Peyronie's disease has been reported in fewer than 1 of 100,000 patients. Musculoskeletal pain, blurred vision, and tinnitus have also been reported.

There have been rare reports of reversible alopecia, agranulocytosis, and dry eyes. Discontinuation of the drug should be considered if any such reaction is not otherwise explicable.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with metoprolol.

Myocardial Infarction

Central Nervous System: Tiredness has been reported in about 1 of 100 patients. Vertigo, sleep disturbances, hallucinations, headache, dizziness, visual disturbances, confusion, and reduced libido have also been reported, but a drug relationship is not clear.

Cardiovascular: In the randomized comparison of metoprolol and placebo described in the CLINICAL PHARMACOLOGY section, the following adverse reactions were reported:

	metoprolol	Placebo
Hypotension (systolic BP < 90 mmHg)	27.4%	23.2%
Bradycardia (heart rate < 40 beats/min)	15.9%	6.7%
Second- or third-degree heart block	4.7%	4.7%
First-degree heart block (P-R ≥ 0.26 sec)	5.3%	1.9%
Heart failure	27.5%	29.6%

Respiratory: Dyspnea of pulmonary origin has been reported in fewer than 1 of 100 patients.

Gastrointestinal: Nausea and abdominal pain have been reported in fewer than 1 of 100 patients.

Dermatologic: Rash and worsened psoriasis have been reported, but a drug relationship is not clear.

Miscellaneous: Unstable diabetes and claudication have been reported, but a drug relationship is not clear.

Potential Adverse Reactions

A variety of adverse reactions not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse reactions to metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (See CONTRAINDICATIONS).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Hypersensitive Reactions: Fever combined with aching and sore throat, laryngospasm, and respiratory distress.

OVERDOSAGE

Acute Toxicity

Several cases of overdosage have been reported, some leading to death.

Oral LD_{50}'s (mg/kg): mice, 1158 to 2460; rats, 3090 to 4670.

Signs and Symptoms

Potential signs and symptoms associated with overdosage with metoprolol are bradycardia, hypotension, bronchospasm, and cardiac failure.

Treatment

There is no specific antidote.

In general, patients with acute or recent myocardial infarction may be more hemodynamically unstable than other patients and should be treated accordingly (see WARNINGS, Myocardial Infarction).

On the basis of the pharmacologic actions of metoprolol, the following general measures should be employed:

Elimination of the Drug: Gastric lavage should be performed.

Bradycardia: Atropine should be administered. If there is no response to vagal blockade, isoproterenol should be administered cautiously.

Hypotension: A vasopressor should be administered, e.g., norepinephrine or dopamine.

Bronchospasm: A beta$_2$-stimulating agent and/or a theophylline derivative should be administered.

Cardiac Failure: A digitalis glycoside and diuretic should be administered. In shock resulting from inadequate cardiac contractility, administration of dobutamine, isoproterenol, or glucagon may be considered.

DOSAGE AND ADMINISTRATION

Hypertension

The dosage of metoprolol tartrate should be individualized. Metoprolol tartrate should be taken with or immediately following meals.

The usual initial dosage is 100 mg daily in single or divided doses, whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after 1 week of therapy. The effective dosage range is 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While once-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, lower doses (especially 100 mg) may not maintain a full effect at the end of the 24-hour period, and larger or more frequent daily doses may be required. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. Beta$_1$ selectivity diminishes as the dose of metoprolol is increased.

Angina Pectoris

The dosage of metoprolol tartrate should be individualized. Metoprolol tartrate should be taken with or immediately following meals.

The usual initial dosage is 100 mg daily, given in two divided doses. The dosage may be gradually increased at weekly intervals until optimum clinical response has been obtained or there is pronounced slowing of the heart rate. The effective dosage range is 100 to 400 mg per day. Dosages above 400 mg per day have not been studied. If treatment is to be discontinued, the dosage should be reduced gradually over a period of 1 to 2 weeks. (See WARNINGS.)

Myocardial Infarction

Early Treatment: During the early phase of definite or suspected acute myocardial infarction, treatment with metoprolol tartrate can be initiated as soon as possible after the patient's arrival in the hospital. Such treatment should be initiated in a coronary care or similar unit immediately after the patient's hemodynamic condition has stabilized.

Treatment in this early phase should begin with the intravenous administration of three bolus injections of 5 mg of metoprolol tartrate each; the injections should be given at approximately 2-minute intervals. During the intravenous administration of metoprolol, blood pressure, heart rate, and electrocardiogram should be carefully monitored.

In patients who tolerate the full intravenous dose (15 mg), metoprolol tartrate tablets, 50 mg every 6 hours, should be initiated 15 minutes after the last intravenous dose and continued for 48 hours. Thereafter, patients should receive a maintenance dosage of 100 mg twice daily (see Late Treatment below).

Patients who appear not to tolerate the full intravenous dose should be started on metoprolol tartrate tablets either 25 mg or 50 mg every 6 hours (depending on the degree of intolerance) 15 minutes after the last intravenous dose or as soon as their clinical condition allows. In patients with severe intolerance, treatment with metoprolol should be discontinued (see WARNINGS).

Late Treatment: Patients with contraindications to treatment during the early phase of suspected or definite myocardial infarction, patients who appear not to tolerate the full early treatment, and patients in whom the physician wishes to delay therapy for any other reason should be started on metoprolol tartrate tablets, 100 mg twice daily, as soon as their clinical condition allows. Therapy should be continued for at least 3 months. Although the efficacy of metoprolol beyond 3 months has not been conclusively established, data from studies with other beta blockers suggest that treatment should be continued for 1 to 3 years.

HOW SUPPLIED:

Metoprolol Tartrate Tablets USP, 50 mg - capsule-shaped, biconvex, white, scored (debossed 166)

Bottles of 100 ..... NDC 57664-166-08
Bottles of 1000 ..... NDC 57664-166-18

Metoprolol Tartrate Tablets USP, 100 mg - capsule-shaped, biconvex, white, scored (debossed 167)

Bottles of 100 ..... NDC 57664-167-08
Bottles of 1000 ..... NDC 57664-167-18

Store between 59° - 86° F (15° - 30° C). Protect from moisture.
Dispense in Tight, Light-resistant Container(USP).

CAUTION: Federal law prohibits dispensing without prescription.

C.S. 5094T01
Iss. 8/96

CARACO PHARMACEUTICAL LABORATORIES, LTD.
DETROIT, MI 48202

509401

Metoprolol Tartrate Tablets, USP

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....50 mg

ISS 9/95

NDC 57664-166-08
NSN 6505-01-090-6797

Metoprolol Tartrate Tablets, USP

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

N 3 57664 16608 6

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....100 mg

ISS 9/95

NDC 57664-167-08
NSN 6505-01-090-6796

Metoprolol Tartrate Tablets, USP

100 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

N 3 57664 16708 3

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....100 mg

ISS 9/95

NDC 57664-167-08
NSN 6505-01-090-6796

Metoprolol Tartrate Tablets, USP

100 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

N 3 57664 16708 3

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....100 mg

ISS 9/95

NDC 57664-167-08
NSN 6505-01-090-6796

Metoprolol Tartrate Tablets, USP

100 mg

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

N 3 57664 16708 3

Pharmacist Information: Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F). Protect from moisture.

Each Tablet Contains:
Metoprolol Tartrate, USP.....100 mg

NDC 57664-167-18
NSN 6505-01-071-6558

Metoprolol Tartrate
Tablets, USP

100 mg

1000 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: Consult accompanying product literature.

N 3 57664 16718 2

ISS 9/95

CARACO PHARMACEUTICAL LABORATORIES, LTD.
DETROIT, MI 48202

UEU 1 0 [illegible]

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....50 mg

ISS 9/95

NDC 57664-166-08
NSN 6505-01-090-6797

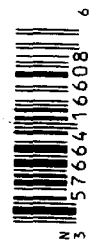
Metoprolol Tartrate Tablets, USP

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.



Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....50 mg

ISS 9/95

NDC 57664-166-08
NSN 6505-01-090-6797

Metoprolol Tartrate Tablets, USP

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

Pharmacist Information:
Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F).
Protect from moisture.

Each Tablet Contains:
Metoprolol
Tartrate, USP .....50 mg

ISS 9/95

NDC 57664-166-08
NSN 6505-01-090-6797

Metoprolol Tartrate Tablets, USP

100 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO PHARMACEUTICAL LABORATORIES, LTD. DETROIT, MI 48202

USUAL DOSAGE:
Consult accompanying product literature.

Pharmacist Information: Container closure is not child-resistant.

Dispense in tight, light-resistant container (USP).

Store between 15°-30°C (59°-86°F). Protect from moisture.

Each Tablet Contains:
Metoprolol Tartrate, USP.....50 mg

NDC 57664-166-18
NSN 6505-01-071-6557

Metoprolol Tartrate
Tablets, USP

1000 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

CARACO
PHARMACEUTICAL
LABORATORIES, LTD.
DETROIT, MI 48202

USUAL DOSAGE: Consult accompanying product literature.

N 57664166185

ISS 9/95

ANDA 74-644

MAY 13 1996

Caraco Pharmaceutical Laboratories, Ltd.
Attention: Annie Holt
1150 Eligah McCoy Drive
Detroit MI 48202

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Metoprolol Tartrate Tablets USP, 50 mg and 100 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be done in 900 mL of SGF w/o enzyme at 37°C using USP 23 apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Metoprolol Tartrate
50 mg & 100 mg tablet
NDA #74-644
Reviewer: J. Lee
74644SA.196

MAY 10 1996

Caraco Pharmaceutical Laboratories
Detroit, Michigan
Submission date:
January 25, 1996

Review of a Study Amendment

This submission contains responses to the deficiencies/comments conveyed to the sponsor in the original review of the fasting/fed studies on the 100 mg tablet.

1. The extraction procedure used in the analytical method was provided as requested. as the internal standard used in the assay of both studies.

2. The method of calculating the recovery for metoprolol and the internal standard was fully explained and the SOP regarding such was submitted as requested. The recovery for metoprolol was:

   The recovery for the internal standard was:

3. The differences in slope values between the first seven standard calibration curves vs the last nine curves due to an instrumentation glitch have been satisfactorily explained.

Comment:

1. All responses to deficiencies/comments in the original bio-review have been satisfactorily addressed.

Recommendation:

1. The bioequivalence studies (fasting and fed) conducted by for Caraco Pharmaceutical Laboratories on its metoprolol tartrate 100 mg tablet, batch #40C12A, comparing it to Lopressor® 100 mg tablet, has been found acceptable by the Division of Bioequivalence. The studies demonstrate that Caraco's metoprolol tartrate 100 mg tablet is bioequivalent (under fasting and fed conditions) to the reference product, Lopressor® 100 mg tablet, manufactured by Geigy Pharmaceutical.

2. The in-vitro dissolution testing data is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The

dissolution testing should be conducted in 900 ml of SGF w/o enzyme at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specification:

Not less than of the labeled amount of the drug in the tablet is dissolved in 30 minutes.

3. The Division of Bioequivalence also agrees that the information submitted by the sponsor demonstrates that metoprolol tartrate 50 mg tablet falls under 21 CFR 320.22 (d)(2) of Bioavailability/Bioequivalence Regulations. The Division of Bioequivalence recommends that the waiver of an in-vivo bioavailability study be granted. Caraco's metoprolol tartrate 50 mg tablet is deemed bioequivalent to Lopressor® 50 mg tablet manufactured by Geigy Pharmaceutical.

4. From the bioequivalence viewpoint the firm has met the requirements of in-vivo bioavailability and in-vitro dissolution testing and the application is acceptable.

C. Lee 5/7/96

J. Lee
Division of Bioequivalence
Review Branch II

for
RD INITIALED RPATNAIK
FT INITIALED RPATNAIK 5/8/96

Concur: Date: 5/10/96

for Keith Chan, Ph.D.
Director, Division of Bioequivalence

Jlee/jl/05-02-96

cc: NDA #74-644 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File

NOV 14 1995

Metoprolol Tartrate
50 mg & 100 mg tablet
NDA #74-644
Reviewer: J. Lee
74644SDW.395

Caraco Pharmaceutical Laboratories
Detroit, Michigan
Submission date:
March 8, 1995

Review of Fasting and Fed in-vivo Bioavailabilty Studies Dissolution Testing Data and a Request for Waiver

Objective:

To assess the rate and extent of absorption of two metoprolol tartrate tablet formulations (Caraco product vs Lopressor®) after administration of single doses to healthy male volunteers under fasted and fed conditions.

Study Design (fed study):

The clinical study (#940089) was conducted at

Eighteen healthy adult male volunteers between the ages of 18-45 years and within ±15% of ideal body weight for his height and frame were entered into the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests of hematologic, hepatic and renal functions. Subjects were excluded if they had any of the following:

*History or presence of significant:

-cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic or psychiatric disease.

More specifically:

-bronchospastic disease
-diabetes
-thryroid disease
-alcoholism or drug abuse within the last year
-hypersensitivity or idiosyncratic reaction to metoprolol or other ß-adrenergic blocking agents.

*Sitting blood pressure less than 110/70 mm Hg at screening or 100/60 mm Hg before dosing. Subjects whose pulse is lower than 50 b.p.m. prior to dosing.

*Subjects on an abnormal diet during the four weeks preceding the study, for whatever reason.

Selected subjects were not to have taken medication (Rx and OTC) for the 7 days preceding the study. Consumption of alcohol or xanthine-containing foods and beverages were prohibited for the 24 hours before dosing and throughout the sample collection period.

Subjects were not allowed to smoke while seated in bed (?).

The study was designed as an open-label, randomized, 3-way crossover comparing the bioavailabilty of Caraco and Geigy's 100 mg metoprolol tartrate tablets under fed conditions and comparing the bioavailability of Caraco's 100 mg test product under fed and fasted conditions. The treatments consisted of a single 100 mg dose of the following products separated by a 7 day washout period between dosings:

Test:	Metoprolol tartrate 100 mg tablet Caraco Pharmaceutical batch #40C12A expiry date: not given
Reference:	Lopressor® 100 mg tablet Geigy Pharmaceutical batch #JT6671 expiry date: Aug 98

Eighteen subjects were dosed according to the following scheme:

	Period I 3 Nov 94	Period II 10 Nov 94	Period III 17 Nov 94
sequence I	C	A	B
sequence II	A	C	B
sequence III	A	B	C
sequence IV	B	C	A
sequence V	B	A	C
sequence VI	C	B	A

sequence I - subj. #1, 2, 8
sequence II - subj. #4, 6, 15
sequence III - subj. #7, 10, 11
sequence IV - subj. #9, 12, 13
sequence V - subj. #16, 17, 18
sequence VI - subj. #3, 5, 14

Regimen A: 1 x 100 mg Caraco product (fasted)
Regimen B: 1 x 100 mg Caraco product (fed)
Regimen C: 1 x 100 mg Lopressor® (fed)

Regimen A: After an overnight fast, subjects were given a 100 mg oral dose of the test product with 240 ml of ambient temperature water.

Data Analysis:

Plasma data was analyzed by the SAS® GLM procedure to detect statistically significant differences ($p<0.05$) between formulations on the untransformed PK parameters; in addition, ln-transformed data were used for analysis for AUC_{0-t}, AUC_{inf} and C_{max}. The analysis of variance model used subjects, period, carryover and drug formulation as factors.

Additionally, ratios of means were calculated using the LSM for both untransformed and ln-transformed AUC_{0-t}, AUC_{inf} and C_{max}. Ratios of means were expressed as a percentage of the LSM for the reference formulation. The comparisons were:

B vs A (test fed vs test fasted)
B vs C (test fed vs ref. fed)

Regimen B & C: After an overnight fast and 30 minutes before their scheduled dosing times, each subject was given a standard breakfast consisting of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 rasher of Canadian bacon, 120 g of hash brown potatoes, 180 ml of orange juice, 240 ml of whole milk. All subjects completed their breakfasts. At their scheduled dosing times, each subject was given their assigned medication with 240 ml of water, according to the randomization scheme.

Blood samples were collected in Vacutainers containing EDTA before dosing (2 x 5 ml) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 18 and 24 hours post-dose (1 x 5 ml). All samples were collected within 2 minutes of the scheduled times. Samples were cooled in an ice bath and centrifuged under refrigeration. The plasma samples were stored in tubes at -12°C or lower, pending assay.

Of the 18 volunteers originally entered into the study, two did not complete the crossover. Subj. #4 was withdrawn from the study by the Medical Designate 6 minutes prior to dosing in period III due to medical events judged to be related to something other than the study drug or procedures. Subj. #13 was withdrawn from the study prior to dosing in period II, since this subject's pre-dose blood pressure was lower than the minimum specified in the protocol. A total of sixteen subjects completed the crossover.

There were two protocol violations in this study. Subj. #14 was dosed despite having a pre-dose blood pressure reading of 109/59 mm Hg in period III. The protocol specified that subjects with a sitting blood pressure lower than 100/60 mm Hg would not be eligible for dosing. Subj. #8 consumed a piece of vanilla cake with chocolate icing approximately 20 hours prior to period III dosing. Neither violation was judged likely to affect the bioavailability comparison.

Several medical events were reported. Subjects #4 and 13 were removed from the study as described above. Subjects #7, 8 and 14 reported non-serious events that were mild in intensity. All medical events are appended.

Analytical: [Not for release under FOI]

Sixteen out of eighteen subjects completed the crossover. The data from seventeen subjects were used in the analysis (subj. #4 completed two legs of the crossover).

Results:

No statistically significant differences were seen in any of the major PK indices on either the untransformed or ln-transformed scales. The ratios of the LSM of the PK parameters are shown below:

		B/A	B/C
(original scale)	AUC_{0-t}	111.4	99.0
	AUC_{inf}	112.1	98.5
	C_{max}	107.2	109.6
(ln-transformed scale)	AUC_{0-t}	115.3	100.5
	AUC_{inf}	115.8	100.7
	C_{max}	108.9	108.2

Study Design (fasting study):

The fasting clinical study (#940088) was conducted at the same facilities and under the same investigators as those used in the fed study. Likewise, the fasting study volunteers underwent the same medical screening and given the same study prohibitions.

The study was designed as an open-label, randomized, two-way crossover comparing the single-dose bioavailability of the test and reference metoprolol tartrate 100 mg formulations (Caraco product vs Lopressor®) under fasted conditions. Thirty-six healthy male volunteers were entered into the study receiving treatments consisting of the same bio-lots of the same formulations used in the fed study. Dosings were separated by a washout period of 7 days.

Thirty-six subjects were dosed according to the following regimen:

	Period I 9 Nov 94	Period II 16 Nov 94
sequence I	A	B
sequence II	B	A

sequence I	subj. #1, 2, 3, 5, 8, 9, 11, 12, 14, 16, 19, 22, 23, 26, 27, 30, 31, 33
sequence II	subj. #4, 6, 7, 10, 13, 15, 17, 18, 20, 21, 24, 25, 28, 29, 32, 34, 35, 36

After an overnight fast, thirty-six subjects were administered a 100 mg dose of the test or reference medication with 240 ml of water. Blood samples were collected, processed and stored in the same manner described in the fed study.

Of the thirty-six volunteers entered into the study, two did not complete the crossover. Subjects #10 and 22 were withdrawn from the study on the morning of the period II dosing, due to medical events (gastroenteritis) judged probably unrelated to the study medication.

Additionally, subjects #6, 7, 8, 13, 26 and 32 experienced mild, non-serious medical events during the study. These events are appended.

There were two deviations from protocol. One subject (#16) was judged eligible for period II dosing even though his pre-dose sitting blood pressure reading (96/64 mm Hg) was slightly lower than the minimum 100/60 mm Hg specified in the protocol. There were 2 minor deviations from the blood sampling schedule (table C2, page 945).

Analytical: [Not for release under FOI]

Data Analysis:
Plasma data was analyzed by the SAS-GLM procedure using the standard ANOVA model. Thirty-four datasets for the subjects who completed the study were used in the statistical analysis.

Results:

No statistically significant differences or sequence effects were seen in any of the pharmacokinetic indices on the untransformed scale; neither were they observed on the ln-transformed scale for the major pharmacokinetic parameters. Mean differences between the test and reference products for AUC were 4.8% for AUC_{0-t} and 3.8% for AUC_{inf}. The mean C_{max} for the test formulation was 2.4% higher than that for Lopressor®. The 90% confidence intervals for the major pharmacokinetic parameters are presented below:

		90% CI n=34
original scale	AUC_{0-t}	[100.1; 109.5]
	AUC_{inf}	[99.7; 107.9]
	C_{max}	[98.1; 106.8]
ln-transformed scale	AUC_{0-t}	[101.0; 113.1]
	AUC_{inf}	[100.7; 111.2]
	C_{max}	[98.5; 110.3]

In-vitro Dissolution:

Dissolution testing was conducted on the bio-lots of the test and reference products. Dissolution testing was also conducted on the 50 mg Caraco product vs Lopressor®, 50 mg, to partially support the waiver request for the 50 mg tablet. The resultant summaries are attached.

Batch Size:

The batch size of the test product used in the bio-study was units (actual yield).

Comment:

1. The laboratory has not submitted the extraction procedure used in the analytical method. The laboratory should provide the procedure. The laboratory should also indicate what internal standard was used in the assays.

2. The method of calculating the recovery for metoprolol and the internal standard is confusing. On pages 569, 601 and 602 of vol. 1.3 are internal standard recovery calculations for three different concentrations. The calculations are seemingly dissimilar, except for those on pages 601 and 602. The laboratory should explain what values 'peak ratio' refers to. The laboratory should also explain how the recovery for metoprolol, page 568, vol. 1.3, is obtained. The SOP for recovery of analytes from biological fluids (#Al-G-1540), as mentioned on page 657, should be submitted.

3. In the fasting study the laboratory should explain why the slopes for the last nine curves (CUH15-CUH23) are

approximately twice that for the first seven curves (CUH08-CUH14).

4. For both studies, the laboratory is requested to submit on a 3½ inch diskette the following information - period, sequence, carryover (as appropriate), treatment (for the pharmacokinetic parameters); and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format.

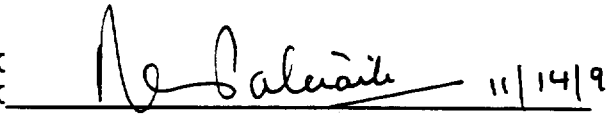
Recommendation:

The bioequivalence studies (fasting and fed) conducted by for Caraco Pharmaceutical Laboratories on their metoprolol tartrate 100 mg tablet, comparing it to Lopressor® 100 mg tablet, is incomplete per comments #1-3.

All comments should be forwarded to the company.

R. Lee 11/14/95

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED RPATNAIK
FT INITIALED RPATNAIK  11/14/95

Concur: See October 17, 1995 memo Date: _____

Keith Chan, Ph.D.
Director, Division of Bioequivalence

JLee/jl/11-8-95

cc: NDA #74-644 (original, duplicate), HFD-630, HFD-600 (Hare), HFD-655 (Lee, Patnaik), HFD-130 (JAllen), HFD-344 (Vish), Drug File, Division File

USP XXIII Apparatus I Basket x Paddle ____ rpm 100

Medium: simulated gastric fluid TS, w/o enzyme Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Lopressor® tablets

Assay Methodology: _____

Results

100 mg

Time (min)	Test Product Lot # 40C12 Mean % Dissolved	Range	(SD)	Reference Product Lot # JT 6671 Mean % Dissolved	Range	(SD)
10	71.0		(1.9)	78.7		(2.3)
20	103.3		(2.7)	101.9		(3.0)
30	104.0		(3.3)	102.2		(2.9)
45	103.7		(3.1)	98.0		(2.9)
			( )			( )
			( )			( )
			( )			( )

50 mg

	Lot # 40C09			Lot # JT 8991		
10	91.4		(2.5)	102.0		(5.2)
20	108.4		(3.0)	104.8		(2.4)
30	108.4		(3.5)	104.2		(2.6)
45	108.9*		(3.1)	104.0		(2.5)
			( )			( )

* Ave. of 11 tabs., excluding tab #3, due to sampling error

Table 1 FED
Project No: 940089
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 17)

	ln AUC 0-t (ng·h/mL)	ln AUCinf (ng·h/mL)	ln Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Caraco (fast) (A)						
Mean	6.65	6.72	4.92482	1.559	0.2106	3.729
SD	0.615	0.601	0.428	0.6094	0.07518	1.4990
CV				39.1	35.7	40.2
n	17	17	17	17	17	17
Caraco (fed) (B)						
Mean	6.73	6.81	4.97340	3.563	0.2009	3.889
SD	0.512	0.513	0.354	1.5478	0.06581	1.6053
CV				43.4	32.8	41.3
n	16	16	16	16	16	16
Geigy (fed) (C)						
Mean	6.76	6.83	4.93044	3.059	0.1944	4.161
SD	0.556	0.560	0.349	1.4883	0.07895	1.7647
CV				48.7	40.6	42.4
n	17	17	17	17	17	17
Least-Squares Means						
Caraco (fast) (A)	6.62	6.69	4.91697			
Caraco (fed) (B)	6.77	6.84	5.00196			
Geigy (fed) (C)	6.76	6.83	4.92285			
Ratio of Least-Squares Means+						
(B/A)%	115.3	115.8	108.9			
(B/C)%	100.5	100.7	108.2			

+ For ln-transformed parameters, this ratio is defined as: 100 * (e raised to the power of x-y), where x and y are the values of ln-transformed parameters for formulation x (test) and y (reference), respectively.

DEFAULT

Table 2 FED
Project No: 940089
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 17)

	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)
Caraco (fast) (A)			
Mean	907.8	969.6	148.7056
SD	520.50	582.81	55.63923
CV	57.3	60.1	37.4
n	17	17	17
Caraco (fed) (B)			
Mean	956.0	1036.3	153.0169
SD	548.31	638.56	52.71454
CV	57.4	61.6	34.5
n	16	16	16
Geigy (fed) (C)			
Mean	996.3	1076.0	146.7840
SD	586.46	674.72	53.39527
CV	58.9	62.7	36.4
n	17	17	17
Least-Squares Means			
Caraco (fast) (A)	884.7	946.9	147.7016
Caraco (fed) (B)	985.9	1061.5	158.2808
Geigy (fed) (C)	996.2	1078.0	144.3793
Ratio of Least-Squares Means			
(B/A)%	111.4	112.1	107.2
(B/C)%	99.0	98.5	109.6

DEFAULT

Table 2 FASTING
Project No: 940088
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 34)

	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)
Caraco (A)			
Mean	804.1	849.3	132.0032
SD	490.19	515.39	51.64214
CV	61.0	60.7	39.1
n	34	34	34
Geigy (B)			
Mean	767.4	818.3	128.8853
SD	505.56	535.80	53.33014
CV	65.9	65.5	41.4
n	34	34	34
Least-Squares Means			
Caraco (A)	804.1	849.3	132.0032
Geigy (B)	767.4	818.3	128.8853
Ratio of Least-Squares Means (A/B)%	104.8	103.8	102.4
90% Confidence Intervals (A/B)%			
lower limit:	100.1%	99.7%	98.1%
upper limit:	109.5%	107.9%	106.8%
p-Value (ANOVA)			
A vs B	0.0955	0.1288	0.3545
Period	0.9079	0.6812	0.8640
Sequence	0.4933	0.5346	0.4895

Table 2
Project No: 940088
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 34)

	AUC 0-t (ng·h/mL)	AUCinf (ng·h/mL)	Cmax (ng/mL)
Power A vs B (REF=B)	>99.9%	>99.9%	>99.9%
Intrasubject CV%	11.2	9.8	10.5

Table 1 FASTING
Project No: 940088
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 34)

	ln AUC 0-t (ng·h/mL)	ln AUCinf (ng·h/mL)	ln Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Caraco (A)						
Mean	6.52	6.58	4.80754	1.588	0.2172	3.466
SD	0.609	0.594	0.401	0.5290	0.06006	1.0764
CV				33.3	27.7	31.1
n	34	34	34	34	34	34
Geigy (B)						
Mean	6.45	6.52	4.76596	1.647	0.2128	3.539
SD	0.639	0.624	0.459	0.5577	0.05615	1.1777
CV				33.9	26.4	33.3
n	34	34	34	34	34	34
Least-Squares Means						
Caraco (A)	6.52	6.58	4.80754			
Geigy (B)	6.45	6.52	4.76596			
Ratio of Least-Squares Means+ (A/B)%	106.8	105.8	104.2			
90% Confidence Intervals (A/B)%						
lower limit:	101.0%	100.7%	98.5%			
upper limit:	113.1%	111.2%	110.3%			
p-Value (ANOVA)						
A vs B	0.0560	0.0633	0.2227			
Period	0.6627	0.7970	0.6965			
Sequence	0.3606	0.3842	0.3576			

\+ For ln-transformed parameters, this ratio is defined as: 100 * (e raised to the power of x-y), where x and y are the values of ln-transformed parameters for formulation x (test) and y (reference), respectively.

Table 1
Project No: 940088
Summary of Results - Metoprolol in Plasma
Mean Pharmacokinetic Parameters
(N = 34)

	ln AUC 0-t (ng·h/mL)	ln AUCinf (ng·h/mL)	ln Cmax (ng/mL)	tmax (h)	kel (1/h)	Half-life (h)
Power						
A vs B (REF=B)	>99.9%	>99.9%	>99.9%			
Intrasubject CV%	13.8	12.1	13.8			

+ For ln-transformed parameters, this ratio is defined as: 100 * (e raised to the power of x-y), where x and y are the values of ln-transformed parameters for formulation x (test) and y (reference), respectively.

USP XXIII Apparatus I Basket x Paddle ____ rpm 100

Medium: simulated gastric fluid TS, w/o enzyme Volume: 900 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Lopressor® tablets

Assay Methodology: _____

Results

100 mg

Time (min)	Test Product Lot # 40C12 Mean % Dissolved	Range	(SD)	Reference Product Lot # JT 6671 Mean % Dissolved	Range	(SD)
10	71.0		(1.9)	78.7		(2.3)
20	103.3		(2.7)	101.9		(3.0)
30	104.0		(3.3)	102.2		(2.9)
45	103.7		(3.1)	98.0		(2.9)
			( )			( )
			( )			( )
			( )			( )

50 mg

	Lot # 40C09			Lot # JT 8991		
10	91.4		(2.5)	102.0		(5.2)
20	108.4		(3.0)	104.8		(2.4)
30	108.4		(3.5)	104.2		(2.6)
45	108.9*		(3.1)	104.0		(2.5)
			( )			( )

* Ave. of 11 tabs., excluding tab #3, due to sampling error